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EXAMINER	
LIU, SUE XU	

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/057,828	LI ET AL.	
	Examiner	Art Unit	
	SUE LIU	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/13/09 has been entered.

Claim Status

2. Claims 23-80 have been cancelled.

Claims 1-22 are currently pending.

Claims 1-22 are being examined in this application.

Election/Restrictions

3. Applicant election without traverse of Group I invention (claims 1-22) on 11/20/2003) is as previously acknowledged.

Claim Objection(s) / Rejection(s) Maintained

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Kauffman and Morris

6. Claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Kauffman** et al. (WO 00/04196) (Date of Patent is January 27, 2000) (see 3/11/04 IDS) and **Morris** et al. (US Patent No. 6,458,530)(Filing Date is April 4, 1996; cited previously). The previous rejection is maintained for the reasons of record as set forth in the previous Office action as well as for the reasons below.

The instant claim recites "An aqueous composition consisting essentially of a library of nucleic acid constructs, each construct in the library comprising:

a cis-element sequence comprising one or more copies of a cis element to which a specified transcription factor is known to bind, the cis element sequence varying within the library of nucleic acid constructs;

a promoter sequence 3' relative to the cis element sequence;

a reporter sequence 3' relative to the promoter sequence, the reporter sequence comprising a variable sequence that varies within the library of nucleic acid constructs;

wherein each cis element sequence corresponds to a different reporter sequence within the library of nucleic acid constructs.

For ***claim 1***, Kauffman et al. (see entire document) disclose "cis acting nucleic acid elements and methods of use" (e.g., see Kauffman et al., title and abstract), which renders

obvious the claimed invention. For example, Kauffman et al. disclose a composition consisting essentially of a library of nucleic acid constructs each construct comprising a cis-element sequence comprising one or more copies of a cis element to which a specified transcription factor is known to bind (e.g., see claim 38, A plurality of isolated nucleic acid molecule [i.e., a library], each isolated nucleic acid molecule comprising one or more cis acting nucleic acid elements"; see also page 1, lines 29-30, "As an example, regulatory proteins called 'transcription factors' bind to cis acting nucleic acid elements"; see also see also page 2, line 5; see also page 14, last paragraph; see also page 9, paragraph 2; see also pages 5-6).

The transition phrase "consisting essentially of" can be interpreted variously to be open-ended.

See MPEP 2111.03.

""A consisting essentially of' claim occupies a middle ground between closed claims that are written in a consisting of' format and fully open claims that are drafted in a comprising' format." PPG Industries v. Guardian Industries, 156 F.3d 1351, 1354, 48 USPQ2d 1351, 1353-54 (Fed. Cir. 1998). See also Atlas Powder v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); In re Janakirama-Rao, 317 F.2d 951, 137 USPQ 893 (CCPA 1963); Water Technologies Corp. vs. Calco, Ltd., 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988). For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355 ("PPG could have defined the scope of the phrase consisting essentially of' for purposes of its patent by making clear in its specification what it regarded as constituting a material change in the basic and novel characteristics of the invention.")." (emphasis added).

In the instant case, there is no clear indicate "what the basic and novel charateristics

actually are". Thus, the transition phrase "consisting essentially of" is construed as "comprising". Kauffman et al. disclose many compositions interpreted here as "physical mixtures" (see *PIN/NIP, Inc. v. Platte Chemical Co.*, 64 USPQ2d 1344, 1350 (Fed. Cir. 2002) (""We therefore construe the term 'composition' ... to mean a physical mixture")) including, for example, mixtures in equilibrium (e.g., see Kauffman et al., paragraph bridging pages 29 and 30, "For example, in one embodiment of the invention, nucleic acid binding factors bound to nucleic acids in a nucleic acid preparation are contacted [i.e., mixed] with a diverse population of isolated nucleic acids. The nucleic acid binding factors will equilibrate between being bound to the cis acting nucleic acid elements present in the nucleic acid preparation, and the cis acting nucleic acid elements present in the diverse population of isolated nucleic acid molecules."). Another example includes mixtures of protein/dna complexes retained after enzymatic digestion that only contain cis-elements that are known to bind to known transcriptions factors (e.g., see Kauffman et al., page 66, paragraphs 1 and 2, "Digestion of the bait DNA-nuclear protein complexes with such an enzyme selectively cleaves naked bait DNA and spares protein-complexed DNA ... At this stage, the sets of selected bait DNAs are highly enriched in sequences that are capable of binding nuclear proteins and nuclear membrane receptors effectively [i.e., known to bind to transcription factors] ... This yields a first crop of sequences among which known cis-elements are present"). Likewise, the elution of protein/dna complexes from a size exclusion column will also produce mixtures of the aforementioned DNA (e.g., see Kauffman et al., page 31, last paragraph, "nucleic acids bound to nucleic acid binding factors will pass through a chromatography column at a different rate than unbound nucleic acids [and thus be collected a mixture of bound nucleic acids]"). Finally, the isolated nucleic acids on a nitrocellulose filter or

nucleic acid chip could also be considered as a "mixture" of resin/chip w/ the nucleic acid. Thus, Kauffman et al. disclose the claimed compositions whether the claim is interpreted as only containing cis-element sequences to which specified transcription factor are known to bind or not. In addition, Kauffman et al. disclose that the cis element sequence varies within the library of nucleic acid constructs (e.g., see page 13, paragraph 1, "As an example, a population that includes all possible molecules of between 5 and 20 nucleotides in length, including each of the four naturally occurring nucleotides at each position, would have approximately ... 10^{13} different nucleic acid molecules. Such a population ... inherently includes all [i.e., known and unknown] possible cis acting nucleic acid elements of up to about 20 nucleotides in length"; see also page 8, first full paragraph; see also page 11, last paragraph; see also page 50, first full paragraph; see also page 22, paragraph 1, "The isolated nucleic acid molecules or the nucleic acid binding factors, or both ... can be biased populations that include cis acting nucleic acid elements ... that are known."). Please note that after a selection process as noted above (e.g., enzymatic digestion, elution from size exclusion column, etc.) only those sequences that bind to a transcription factor would be left. Kauffman et al. also disclose a promoter sequence 3' relative to the cis element sequence (e.g., see page 9, last paragraph, "A cis acting nucleic acid element can be localized within the nucleic acid sequence it regulates, or upstream or downstream thereof"; see also page 3, paragraph 1). Kauffman et al. also disclose a reporter sequence 3' relative to the promoter sequence (e.g., page 14, first full paragraph, "If desired, some or all of the isolated nucleic acid molecules can ... be flanked at one or both ends [i.e., both 3' and 5'] by ... detectable sequences [i.e., reporter molecules]"; see also paragraph bridging pages 50-51, "... a plurality of isolated nucleic acid molecules containing cis acting nucleic acid elements can

be … enhancers and promoters … or any other set of nucleic acid cis acting elements"). Finally, Kauffman et al. also disclose cis element sequences that "corresponds" to a given reporter sequence within the library of nucleic acid constructs (e.g., see page 14, first full paragraph; see also paragraph 19, lines 13-14; see also page 34, middle paragraph; see also page 35, paragraphs 1-3; see also page 60 paragraph 1 which disclose numerous methods of detection using reporter sequences that "correspond" to the cis element i.e., allow identification of the cis element).

For ***claims 2 and 3***, Kauffman et al. disclose the composition according to claim 1 wherein the reporter sequences comprise priming sequences 5' and 3' relative to the variable sequences including conserved sequences (e.g., see e.g., see page 14, first full paragraph, "If desired, some or all of the isolated nucleic acid molecules can include, or be flanked at one or both ends by, known sequences, such as sequences homologous to oligonucleotide primers for the polymerase chain reaction (PCR); see also page 25, last paragraph; see also page 33, first paragraph").

For ***claims 4-7***, Kauffman et al. disclose the composition according to claim 1 wherein the library comprises at least 100 different cis elements (e.g., see Kauffman et al. page 13, line 25 wherein 10^{13} different cis elements are disclosed).

For ***claims 8-10***, Kauffman et al. disclose the composition according to claim 1 with at least two copies of the cis element (e.g., see claim 38, "A plurality of isolated nucleic acid molecules, each isolated nucleic acid molecule comprising one or more [i.e., two, three, four, etc.] cis acting nucleic acid elements"; see also page 57, lines 24-25).

For ***claims 11-13***, Kauffman et al. disclose the composition according to claim 1 with cis elements with a length between 5 and 50 base pairs (e.g., see page 10, first full paragraph, "A cis

acting nucleic acid element is generally from about 4 to about 100 nucleotides in length, and is more typically from about 6 to about 25 nucleotides in length").

For ***claim 20***, Kauffman et al. disclose the composition according to claim 1 wherein different reporter sequences encode different reporter proteins (e.g., see page 3, paragraph 1; see also page 47, paragraph 1; see also column 6, paragraph 3, "see column 3, lines 46-53, "The methods are advantageous in providing a means for simultaneously identifying nucleic acid binding factors that modulate a genetic activity of a plurality of nucleic acids").

The prior art teaching of Kauffman et al. differs from the claimed invention as follows:

For ***claim 1***, the prior art teachings of Kauffman et al. differ from the claimed invention by not specifically reciting the use of a variable region within the reporter sequence nor does Kauffman et al. teach that each cis element sequence must correspond to a different reporter sequence within the library of nucleic acid constructs. Kauffman et al. only teach the use of the same reporter sequence. In addition, the Kauffman reference does not explicitly states the "an aqueous composition" consisting essentially of a "library of nucleic acids".

For ***claims 14-19***, the prior art teachings of Kauffman et al. differ from the claimed invention by not specifically reciting the size of the variable sequence in the reporter e.g., at least 14 bases in length (see claim 14).

For ***claims 21-22***, the prior art teachings of Kauffman et al. do not explicitly recite an "open reading frame" although it is undoubtedly implied from the molecular cloning techniques used i.e., the reporter wouldn't be expressed without it (e.g., see column 23, line 48).

However, Morris et al. and/or Kauffman et al. teach the followings:

For ***claims 1 and 14-19***, Morris et al. (see entire document) disclose specially selected nucleic acid tags that contain different variable regions between 8 and 150 nucleotides in length for labeling molecular, cellular and viral libraries which would encompass the nucleic acid constructs of Kauffman et al. (e.g., see Morris et al., Summary of Invention; see also column 3, paragraphs 2-3; see also claim 7). Morris et al. further disclose, in addition to the teachings noted above for Kauffman et al., that the tagged libraries may be in the form of a composition (e.g., see abstract, "Methods of selecting tag nucleic acids and VLSIPS^{TM} arrays and the arrays made by the methods are used to label and track compositions, including cells and viruses, e.g., in libraries of cells or viruses. In addition to providing a way of tracking compositions in mixtures, the tags facilitate analysis of cell and viral phenotypes."; see also field of invention; see also column 4, paragraphs 1-4; see especially column 2, second full paragraph, "For instance, as explained herein, all of the members of a cellular library can be tested for response to an environmental stimulus using a mixture [i.e., a composition] of all of the members of the cellular library in a single assay. This is accomplished, e.g., by labeling each member of the cellular library, e.g., by cloning a nucleic acid tag into each cell type in the library, mixing each cell type in the library in an appropriate solution, and exposing part of the solution to the selected environmental stimulus."). Please note that the term "composition" has been held to represent a "physical mixture" by the Federal Circuit. See *PIN/NIP, Inc. v. Platte Chemical Co.*, 64 USPQ2d 1344, 1350 (Fed. Cir. 2002) (""We therefore construe the term 'composition' ... to mean a physical mixture").

In addition, Kauffman et al., teaches compositions consisting essentially of "a library of nucleic acids" (e.g. claim 38). The reference also teaches various buffers and/or solutions can be

used for making the DNA library. For examples, the reference teaches using aliquots (i.e. aqueous solutions) of DNA solutions for various cloning procedures (e.g. p.66); the reference teaches various buffers can be used for (binding interactions; p.29), which the buffers read on aqueous compositions; the reference also teaches acceptable pharmaceutical carriers include "aqueous solutions" (e.g. p.55, lines 10+); the reference also teaches using PCR to amplify DNA (e.g. p.65), which the PCR inherently requires "aqueous solutions"; the reference further teaches ligating DNA fragments into vectors as well as subsequent cloning steps (e.g. p.65), which steps are all require aqueous solutions without evidence to the contrary.

Similarly, Morris et al. also teach placing DNA molecules in various aqueous solutions/buffers. For examples, the Morris reference teaches mixing cells containing a DNA library in solutions (e.g. col.2, ll.30+); the Morris reference also teaches hybridizing the library of DNA to probes in hybridization solutions (e.g. col.2, ll.30+; cols.9-10), which the hybridization solution reads on aqueous composition; the Morris reference further teaches various manipulation techniques of DNA in solutions (e.g. col.21, lines 4+).

For ***claim 21***, Morris et al. disclose the use of open reading frames (e.g., see column 11, paragraph 3; see also example 1, especially column 24, lines 14-51).

For ***claim 22***, both Morris et al. and Kauffman et al. do not explicitly state that a stop codon is 3' relative to the reporters disclosed therein, but the Examiner contends that stop codons are typically used in the art and the reporter sequence would not have the proper length if it did not contain such a stopping point. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The

Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to generate an aqueous composition consisting essentially of a library of nucleic acid constructs.

A person of ordinary skill in the art would have been motivated at the time of the invention to place the nucleic acid constructs in aqueous solution, because both Kauffman and Morris teach it is routine and known in the art to place DNA in aqueous solutions (such as various buffers) so that the DNA can be stably stored and/or used for subsequent reactions (such as PCR, ligation, cloning, etc.). It would have been obvious to one of ordinary skill in the art to apply the standard technique of manipulating various DNA molecules (such as a nucleic acid library) in various aqueous buffer solutions as taught by Kauffman and Morris, to optimize the DNA library for the predicable result of enabling standard DNA processing and/or storage.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make and use the variable reporters as taught by Morris et al. with the cis acting nucleic acid library as taught by Kauffman et al. because Kauffman et al. explicitly state, "[n]ucleic acid chips and automated detection procedures are particularly advantageous in high-throughput screening procedures for identifying cis acting nucleic acid elements" (e.g., see Kauffman et al., column 16, lines 53-54), which would encompass the automated nucleic acid chips disclosed by Morris et al. i.e., the references represent analogous art (e.g., see Morris et al., figure 5 disclosing a nucleic acid chip). Furthermore, one of ordinary skill in the art would have

been motivated to use the variable reporters as taught by Morris et al. because the variable reporters "provide a much more cost-effective approach to screening" (e.g., see Morris et al., column 11, lines 60-62) and facilitate "massive parallel analysis" (e.g., see Morris et al., Summary of Invention), which would improve upon the high throughput screening embodiments disclosed by Kauffman. In addition, less "ambiguities" would result in the high throughput screening assay when using the reporters disclosed by Morris et al. (e.g., see column 2, last paragraph and column 3, paragraphs 1-2, "In one class of embodiments, the invention provides a method of selecting a set of tag nucleic acids designed for minimal cross hybridization to a VLSIPS™ array … because it reduces ambiguities in the interpretation of hybridization results which arise due to multiple nucleic acid species binding to a single species of probe on the VLSIPS™ array"). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because both Morris et al. and Kauffman et al. teach the use of "cloning" techniques to produce the nucleic acid libraries (e.g., compare Kauffman et al., page 50, last paragraph, "The plurality can be produced in abundance by, for example, chemical synthesis or by amplification by the polymerase chain reaction" to Morris et al., "Also, because the methods of using the arrays and tags optionally include PCR, LCR and other in vitro amplification techniques for amplifying tag nucleic acids, the kits of the invention optionally include reagents for practicing in vitro amplification methods such as taq polymerase"). Furthermore, Kauffman et al. explicitly state, "[n]ucleic acid chips and automated detection procedures are particularly advantageous in high-throughput screening procedures for identifying cis acting nucleic acid elements" (e.g., see Kauffman et al., column 16, lines 53-54), which would encompass the automated nucleic acid chips disclosed by Morris et al. (e.g., see Morris et al., figure 5 disclosing

a nucleic acid chip).

Alternatively, the Examiner contends that the mere substitution of one reporter for another, which are both known in the art for labeling nucleic acids, would lead to the same predictable result in this case, namely, identification of the cis-elements. Thus, even if, *assuming arguendo*, Kauffman et al. did not provide motivation (which is not the case, see above) such a substitution would still be obvious in light of the Supreme Court *KSR* decision. *KSR Int'l Co. v. Teleflex Inc No.*, 550 U.S._____, 82 USPQ2d 1385, 1396 (S.Ct. Apr 30, 2007).

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since Kauffman et al and Morris et al have demonstrated the success of generating various DNA vectors comprising all the required elements, and various methods of successful DNA manipulations.

Response

7. Applicants' arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the reasons set forth below. Please note that the above rejection has been modified from its original version to more clearly address applicants' new arguments and claim amendments.

[1] Applicants argue there is no reasonable expectation of success. (Reply. p.6).

[1] Applicants are respectfully directed to the above rejection for statements of reasonable expectation of success. Applicants have not provided any reason or factual evidence to indicate

"unpredictability". The only reasoning in the Remark (Reply, p.6) seems to be of the opinion offered by applicant's representative(s).

> "The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant." (MPEP 716.01(c) II).

In addition, applicants argument of "unpredictability" seems to be hinged on "transcription factor analysis", which is not a feature recited in the instant claims. The instant claims are drawn to a product of "a library of nucleic acids" containing various elements.

[2] Applicants argue "the art must contain some suggestion or motivation to combine these elements. (Reply, pp.6-7).

[2] Applicants are respectfully directed to the recent Supreme Court decision, which forecloses the argument that a specific teaching, suggestion, or motivation in the art is required to support a finding of obviousness. KSR, 127 S.Ct. at 1741, 82 USPQ2d at 1396. Applicants are also respectfully directed to the above rejection for reasons to combine the cited references.

[3] Applicants also seem to argue hindsight reasoning. (Reply, p.6).

[3] In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed

invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

[4] Applicants also argue the Kauffman and the Morris references do not teach "cis elements to which a specified transcription factor is known to bind". (Reply, p.7).

[4] First, the transition phrase "consisting essentially of" is interpreted as open-ended (see discussion supra), which does not preclude the use of additional cis elements that are not "known to bind" in the mixture. That is, only the "library" need contain members with this requirement. Other substituents, including nucleic acids, in the mixture which are not considered to be "part of the library" can thus contain cis elements that are not known to bind. Thus, Applicants' arguments are not commensurate in scope with the claims. Further, even if, assuming arguendo, the claims could be fairly interpreted as suggested by Applicants Kauffman et al. disclose such a library. For example, when the library is digested with an enzyme, only the members "known to bind" are left behind (see Kauffman et al., page 66, paragraphs 1 and 2, "Digestion of the bait DNA-nuclear protein complexes with such an enzyme selectively cleaves naked bait DNA and spares protein-complexed DNA … At this stage, the sets of selected bait DNAs are highly enriched in sequences that are capable of binding nuclear proteins and nuclear membrane receptors effectively [i.e., known to bind to transcription factors] … This yields a first crop of sequences among which known cis-elements are present). Likewise, the elution of protein/dna complexes from a size exclusion column would also produce the claimed mixtures (e.g., see Kauffman et al., page 31, last paragraph, "nucleic acids bound to nucleic acid binding factors

will pass through a chromatography column at a different rate than unbound nucleic acids [and thus be collected a mixture of bound nucleic acids]").

In addition, the Kauffman reference also teaches the transcription factors and cis acting elements can be known. (e.g. p.18, lines 1+; p.66, lines 15; p.62). Thus, at least, it would have been obvious for one of ordinary skill in the art to generate vectors comprising "known" (or predetermined) cis-element (with a known binding transcription factor).

Li and Morris

8. Claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al. (WO 00/34435) (Date of Patent is **June 15, 2000**) and Morris et al. (US Patent No. 6,458,530) (Filing Date is **April 4, 1996**) (of record). The previous rejection is maintained for the reasons of record as set forth in the previous Office action as well as for the reasons below.

For ***claim 1***, Li et al. (see entire document) teach cis-element reporter constructs and uses thereof including "high throughput" screening libraries (e.g., see abstract; see also example 4), which renders obvious the claimed invention. For example, Li et al. disclose a library of nucleic acid constructs (e.g., see figure 4A/B wherein a library of "SEAP" constructs are disclosed including Ap1, HRE, Myc, p53, etc.). In addition, Li et al. disclose constructs comprising a cis-element sequence comprising one or more copies of a cis element to which a specified transcription factor is known to bind (e.g., see Li et al., pages 9-10, Example 1, The following cis elements were utilized for constructing cis-acting reporters: NF-kb … HRE … Myc … p53 … [etc.]"; see also page 10, last paragraph, "In a AP1-SEAP construct, the cis element in the construct contains six copies of AP1 … In a SRE-SEAP construct, the construct contains three

copies of SRE element … [etc.]"). Li et al. also disclose that the cis element sequence varying within the library of nucleic acid constructs (e.g., see figure 4 A/B disclosing, for example, Ap1, HRE, Myc, p53, etc.). Li et al. also disclose a promoter sequence 3' relative to the cis element sequence (e.g., see Summary of Invention, "In one embodiment of the present invention, there is provided a cis element-reporter construct comprising a cis element, a reporter gene and a promoter"; see also figures 1-3 showing, for example, 3' orientation of the TK promoter relative to the KB4 cis element; see also Examples). Li et al. also disclose a reporter sequence 3' relative to the promoter sequence (e.g., see figures 1-3 showing SEAP, d2EGFP and luciferase reporters in a 3' position relative to the cis element, respectively; see also Examples). Finally, Li et al. disclose a "correspondence" between each cis element sequence and a given reporter sequence within the library (e.g., see figure 4A/B, wherein the amount of SEAP activity is shown to "correspond" to the type of cis element under various conditions).

For ***claims 4 and 5***, Li et al. disclose the composition according to claim 1 wherein the library comprises at least 20 different cis elements (e.g., see Example 2 and figure 4 wherein Li et al. disclose a library of 33 cis elements including 6 (AP1) + 3 (SRE) + 3 (CRE) + 3 (GRE) + 3 (HRE) + 4 (NF-kB) + 3 (NFAT) + 6 (myc) + 2 (p53)).

For ***claims 8-10***, Li et al. disclose the composition according to claim 1 wherein the cis element sequence comprises at least four copies of the cis element (e.g., see Example 2 and figure 4 A/B wherein the AP1 construct, for example, contains "six" copies).

For ***claims 11-13***, Li et al. disclose the composition according to claim 1 wherein an individual copy of the cis element has a length between about 5 and 50 base pairs (e.g., see Li et al., page 9, lines 6-7 wherein, for example, NF-kB with 40 base pairs is disclosed).

For ***claim 20***, Li et al. disclose the composition according to claim 1 wherein the different reporter sequences encode different reporter proteins (e.g., see figures 1-3 disclosing SEAP, d2EGFP and luciferase, respectively).

The prior art teachings of Li et al. differ from the claimed invention as follows:

For ***claim 1***, Li et al. fail to disclose a "composition" that comprises the library. Li et al. only disclose the use of "separate" library members transfected into different cell lines on microtiter plates (e.g., see Example 8, especially page 17, line 18 wherein 12 and 24 well plates are disclosed; see also Example 4, page 12, second to last paragraph, "Establishment of stable cell lines that express individual reporters expands application of this cis-element reporter in the cell-based high throughput drug screening."). In addition, the Li reference does not explicitly states the "an aqueous composition" consisting essentially of a "library of nucleic acids".

For ***claims 2-3***, Li et al. fail to disclose "priming sequences" 5' and 3' to the variable sequences.

For ***claims 6-7***, Li et al. fail to disclose a library with at least 50 cis elements. Li et al. only disclose a library of 33 cis elements.

For ***claims 14-19***, Li et al. fail to disclose the size of the variable sequence in the reporter.

For ***claims 21-22***, Li et al. fail to explicitly recite an "open reading frame" although it is undoubtedly implied from the molecular cloning techniques used i.e., the reporter wouldn't be expressed without it (e.g., see figures and Examples).

However, Morris et al. teach the following limitations:

For ***claim 1***, Morris et al. (see entire document) disclose, in addition to the cumulative teachings noted above for Li et al, specially selected nucleic acid tags that contain variable

regions between 8 and 150 nucleotides in length for labeling molecular, cellular and viral libraries which would encompass the nucleic acid constructs of Li et al. (e.g., see Morris et al., Summary of Invention; see also column 3, paragraphs 2-3; see also claim 7). Thus, even if, *assuming arguendo*, Li et al. did not disclose this limitation (which is not the case, see above), this deficiency would be remedied by Morris et al. Morris et al. further disclose, in addition to the teachings noted above for Kauffman et al., that the tagged libraries may be in the form of a composition (e.g., see abstract, "Methods of selecting tag nucleic acids and VLSIPS^{TM} arrays and the arrays made by the methods are used to label and track compositions, including cells and viruses, e.g., in libraries of cells or viruses. In addition to providing a way of tracking compositions in mixtures, the tags facilitate analysis of cell and viral phenotypes."; see also field of invention; see also column 4, paragraphs 1-4; see especially column 2, second full paragraph, "For instance, as explained herein, all of the members of a cellular library can be tested for response to an environmental stimulus using a mixture [i.e., a composition] of all of the members of the cellular library in a single assay. This is accomplished, e.g., by labeling each member of the cellular library, e.g., by cloning a nucleic acid tag into each cell type in the library, mixing each cell type in the library in an appropriate solution, and exposing part of the solution to the selected environmental stimulus."). Please note that the term "composition" has been held to represent a "physical mixture" by the Federal Circuit. See *PIN/NIP, Inc. v. Platte Chemical Co.*, 64 USPQ2d 1344, 1350 (Fed. Cir. 2002) (""We therefore construe the term 'composition' … to mean a physical mixture").

In addition, Morris et al. also teach placing DNA molecules in various aqueous solutions/buffers. For examples, the Morris reference teaches mixing cells containing a DNA

library in solutions (e.g. col.2, ll.30+); the Morris reference also teaches hybridizing the library of DNA to probes in hybridization solutions (e.g. col.2, ll.30+; cols.9-10), which the hybridization solution reads on aqueous composition; the Morris reference further teaches various manipulation techniques of DNA in solutions (e.g. col.21, lines 4+).

For ***claims 2-3***, Morris et al. disclose priming sites 5' and 3' to the reporter sequences (e.g., see figure 5 caption, "Tags were amplified using a single pair of primers that are homologous to the common priming sites which flank each tag [i.e., 5' and 3']").

For ***claims 6-7***, Morris et al. disclose "massive parallel analysis" (e.g., see Morris et al., Summary of Invention), which would render obvious larger numbers of constructs in order to "provide a much more cost-effective approach to screening" than the "12 or 24-well" approach disclosed by Li et al. (e.g., compare Morris et al., column 11, lines 60-62, "Even if the analysis were carried out in a parallel fashion using, e.g., 96-well plates, the effort required to plate, organize, label and track each clone would be prohibitive. The present invention provides a much more cost-effective approach to screening cells" to Li et al., Example 8, "The activity assay of the present invention may be carried out in a 12 or 24 well plate"; see also column 4, first full paragraph, "In preferred embodiments, the set of tag nucleic acids comprises from 100-100,000 tags. Typically, a tag set will include between about 500 and 15,000 tags. Usually, the number of tags in a tag set is between about 5,000 and about 14,000 tags")

For ***claims 14-19***, Morris et al. disclose specially selected nucleic acid tags that contain variable regions between 8 and 150 nucleotides in length for labeling molecular, cellular and viral libraries that would encompass the nucleic acid constructs of Li et al. (e.g., see Morris et al., Summary of Invention; see also column 3, paragraphs 2-3; see also claim 7).

For ***claim 21***, Morris et al. disclose the use of open reading frames (e.g., see column 11, paragraph 3; see also example 1, especially column 24, lines 14-51).

For ***claim 22***, Morris et al. does not explicitly state that a stop codon is 3' relative to the reporters disclosed therein, but the Examiner contends that stop codons are typically used in the art and the reporter sequence would not have the proper length if it did not contain such a stopping point. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

A person of ordinary skill in the art would have been motivated at the time of the invention to place the nucleic acid constructs in aqueous solution, because Morris et al. teach it is routine and known in the art to place DNA in aqueous solutions (such as various buffers) so that the DNA can be stably stored and/or used for subsequent reactions (such as PCR, ligation, cloning, etc.). It would have been obvious to one of ordinary skill in the art to apply the standard technique of manipulating various DNA molecules (such as a nucleic acid library) in various aqueous buffer solutions as taught by Morris et al., to optimize the DNA library for the predicable result of enabling standard DNA processing and/or storage.

It would have been *prima facie* obvious to of ordinary skill in the art at the time the invention was made to make and use the variable reporters as taught by Morris et al. with the cis acting nucleic acid libraries as taught by Li et al. because Morris et al. explicitly state that their

sequences can be used to track, for example, recombinant cells in high throughput screening assays (e.g., see Morris et al., "This invention provides sets of nucleic acid tags, arrays of oligonucleotide probes, nucleic acid-tagged sets of recombinant cells ..."), which would encompass the high throughput screening of recombinant cells disclosed by Li et al. (e.g., see Li et al., Example 4, "A set of d2EGFP reporters with different cis-elements were generated, which are used for monitoring different transcription factors. Establishment of stable cell lines that express individual reporters expands application of this cis-element reporter in the cell-based high throughput drug screening"; see also Example 5, "cell clones can be used in cell based high-throughput screening in search of factors involved in cAMP signal transduction pathway"). Furthermore, one of ordinary skill in the art would have been motivated to use the variable reporters as taught by Morris et al. because the variable reporters "provide a much more cost-effective approach to screening" than the "12 or 24-well" approach disclosed by Li et al. (e.g., compare Morris et al., column 11, lines 60-62, "Even if the analysis were carried out in a parallel fashion using, e.g., 96-well plates, the effort required to plate, organize, label and track each clone would be prohibitive. The present invention provides a much more cost-effective approach to screening cells" to Li et al., Example 8, "The activity assay of the present invention may be carried out in a 12 or 24 well plate") and facilitate "massive parallel analysis" (e.g., see Morris et al., Summary of Invention), which would improve upon the high throughput screening embodiments disclosed by Li et al. In addition, less "ambiguities" would result in the high throughput screening assay when using the reporters disclosed by Morris et al. (e.g., see column 2, last paragraph and column 3, paragraphs 1-2, "In one class of embodiments, the invention provides a method of selecting a set of tag nucleic acids designed for minimal cross

hybridization to a VLSIPS™ array … because it reduces ambiguities in the interpretation of hybridization results which arise due to multiple nucleic acid species binding to a single species of probe on the VLSIPS™ array"). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because both Morris et al. and Li et al. teach general "cloning and expression" methods for both RNA and DNA that can used to create/track cellular libraries (e.g., see Morris et al., column 20, last paragraph, "Molecular cloning and expression techniques for making biological and synthetic oligonucleotides and nucleic acids are known in the art. A wide variety of cloning and expression and in vitro amplification methods suitable for the construction of nucleic acids are well-known to persons of skill"; see also column 8, line 29; see also column 9, last full paragraph; see also column 20, last paragraph; also Li et al., Summary of Invention, "In yet another embodiment of the present invention, there is provided a method of monitoring activation of a transcription factor, comprising the steps of … transfecting a cell line with the vector; and detecting expression of the reporter gene, wherein expression of the reporter gene indicates activation of the transcription factor").

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since Li et al and Morris et al have demonstrated the success of generating various DNA vectors comprising all the required elements, and various methods of successful DNA manipulations.

Response

9. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed

persuasive for reasons set forth below. Please note that the above rejection has been modified from it original version to more clearly address applicants' new arguments and claims.

[1] Applicants argue there is no reasonable expectation of success. (Reply. p.6).

[1] Applicants are respectfully directed to the above rejection for statements of reasonable expectation of success. Applicants have not provided any reason or factual evidence to indicate "unpredictability". The only reasoning in the Remark (Reply, p.6) seems to be of the opinion offered by applicant's representative(s).

> "The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant." (MPEP 716.01(c) II).

In addition, applicants argument of "unpredictability" seems to be hinged on "transcription factor analysis", which is not a feature recited in the instant claims. The instant claims are drawn to a product of "a library of nucleic acids" containing various elements.

[2] Applicants argue "the art must contain some suggestion or motivation to combine these elements. (Reply, pp.6-7).

[2] Applicants are respectfully directed to the recent Supreme Court decision, which forecloses the argument that a specific teaching, suggestion, or motivation in the art is required to support a finding of obviousness. KSR, 127 S.Ct. at 1741, 82 USPQ2d at 1396. Applicants are also respectfully directed to the above rejection for reasons to combine the cited references.

[3] Applicants also seem to argue hindsight reasoning. (Reply, p.6).

[3] In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

[4] Applicants argue the constructs of Li are not grouped together in this manner. (Reply, p.7).

[4] In response to applicant's arguments against the Li et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, the combined teachings of

Li et al. and Morris et al. clearly teach the limitation of using a mixed composition as outlined in the newly amended rejection above. For example, a person of skill in the art would realize that Morris et al. would facilitate "massive" parallel screening of mixtures via the "bar coding" techniques set forth therein. That is, a person of skill in the art could monitor multiple transcription factors simultaneous, say by mRNA (or corresponding cDNA) expression, and then "read" the cells that were so stimulated using the arrays set forth in Morris. This would represent a significant time saving advantage of the teachings in Li et al. who were monitoring these sequences (i.e., cloned into cell populations) individually on 12 and 24 microtiter plates.

In addition, applicants are respectfully directed to the above rejections for discussion on how the combination of the cited references (Li and Morris) render the instant claimed invention ("An aqueous composition consisting essentially of a library of nucleic acids) obvious.

New Claim Objection(s) / Rejection(s)

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter Rejection

11. Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 has been amended to recite "An aqueous composition consisting essentially of..." as filed on 1/13/09. However, the instant specification does not provide support for the claimed "aqueous composition consisting essentially of..." The instant specification does not provide support for "an aqueous composition". Further, the term "consisting essentially of" can be interpreted various. For example, the said transition phrase "consisting essentially of" can be narrowly construed to mean only the library plus other reagents that do not "materially effect the basic and novel characterists of the claimed invention". (see MPEP 2111.03). However, the instant specification does not provide support for such a composition.

If Applicant believes this rejection is in error, applicant must disclose where in the specification support for the entire scope of the amendment(s) and/or new claims can be found. As a result, Claim 1 and its dependent claims (2-22) represent new matter.

Second paragraph of 35 U.S.C. 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claim 1 recites "which a specific transcription factor is known to bind". The term "known" in claim 1 is a relative term which renders the claim indefinite. The term "known" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The recitation of "which a specific transcription factor is known to bind" renders the instant claim indefinite and the said claim language can be interpreted variously. The instant specification does not specifically define the term "known" to be of any time frame or to any particular entity. It is not clear when or to whom (what) the concept of "known" is relative. For example, it is not clear if the cis element is "known" to bind to a specific transcription factor at the time of filing of the instant application, or at any other time. It is also not clear if the cis element bind to a specific transcription factor by what entity. That is the cis element might be "known" to bind to a specific transcription factor to one experimenter, but may not be "known" to bind the transcription factor by another experimenter. Thus, one of ordinary skill in the art would not apprise the metes and bounds of the instant claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Sue Liu/
Patent Examiner, AU 1639
3/17/09